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GAU 1655

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Riviere et al.

Appln. No.: 08/252,710 Group Art Unit: 1655

Filed: 2 June 1994 Examiner: J. Fredman

For: RETROVIRAL GENE THERAPY VELTORS AND THERAPEUTIC METHODS BASED THEREON

APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellants submit the following:

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I. REAL PARTIES IN INTEREST

The real parties in interest are the co-assignees, Whitehead Institute for Biomedical Research and Cell Genesys, Incorporated.

II. RELATED APPEALS AND INTERFERENCES

Appellants, assignees and the undersigned are unaware of any related appeals or interferences that could have a direct affect on, could be affected directly by or have a bearing on the instant appeal.

III. STATUS OF CLAIMS

The instant application was filed with 34 claims.

Claims 32-34 were withdrawn from consideration in the Office Action of August 1995 as a result of the election of Group I containing claims 1-31 of the Restriction Requirement of 6 April 1995.

Claims 5 and 32-34 were cancelled and claims 35-37 were added in the Amendment filed 20 November 1995.

Claims 38-41 were added in the Amendment filed 18 February 1997.

Claims 42-44 were added in the Amendment filed 10 June 1999.

In the Office Action mailed 27 January 1999, Claims 38-41 were indicated to be allowable.

Claims 38-41 are allowable.

Claims 1-4, 6-31, 35-37 and 42-44 are on appeal.

IV. STATUS OF AMENDMENTS

An Amendment Under 37 C.F.R. 1.116 was mailed 20 December 1999. In the Advisory Action mailed 29 February 2000, that Amendment was not entered. A second Amendment Under 37 C.F.R. 1.116 was filed 27 March 2000. As noted in the second Advisory Action of 3 April 2000, the second Amendment After Final filed 27 March 2000 was not entered.

V. SUMMARY OF THE INVENTION

The claims on appeal relate to recombinant retroviral vectors, see the title. The vectors are an assemblage of various elements including a splice donor site (page 15 of the instant specification, line 3), a packaging site (page 16, line 23) and a splice acceptor site (page 15, lines 3-4). The vectors do not contain a selectable marker (page 15, lines 14-15) or a complete gag, pol or env gene (page 14, lines 33-34). The vectors are useful for carrying genes of interest and expressing desired levels of the gene products in a wide range of cell types (page 6, lines 24-28).

VI. ISSUE

Claims 1-4, 6-31, 35-37 and 42-44 were rejected under 35 U.S.C. 112, first paragraph in the Final Office Action mailed 19 July 1999 for a perceived deficiency in satisfying the written description requirement for the particular vector element, "consensus splice acceptor site". The Examiner believed there is no basis for that phrase in the original specification.

VII. GROUPING OF CLAIMS

Appealed claims 1-4, 6-31, 35-37, 42 and 43 stand or fall together.

Appealed claim 44 stands or falls alone.

VIII. ARGUMENTS

On page 2 of the Final Office Action mailed 19 July 1999, the appealed claims were rejected under 35 U.S.C. 112, first paragraph. The Examiner believed the claimed subject matter is not described in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

Yet, the Examiner recognized a consensus about the basic GT-AG site in the Office Action mailed 27 January 1999, page 3, full paragraph.

The Examiner maintained that the term represents a broad term, which is not supported by the narrower disclosure of the specification.

The rejection is improper for the following reasons.

THE CLAIMED INVENTION

The invention provided in claims 1-4, 6-31, 35-37, 42 and 43 relates to retroviral vectors for delivering genes to interest to a variety of cell types.

The claims as a whole relate to those vectors.

The vectors of interest contain a variety of elements, such as a splice donor site, a splice acceptor site, LTR sequences and so on.

The specification teaches at page 14, lines 27-29 that the LTR's are derived from a retrovirus of interest. A preferred retrovirus is the Moloney murine leukemia virus.

The specification teaches at page 15, lines 3 and 4, that the vectors of interest can contain a splice donor site and a splice acceptor site. The specification teaches certain sites where the donor and acceptor sites are located.

The specification teaches at page 15, lines 14 and 15 that the vectors generally do not contain selectable markers.

The specification teaches at the bottom of page 15, that vectors of interest can be those in which an enhancer sequence is placed upstream from the alpha globin promoter. As taught at the top of page 16 of the instant specification, the enhancer can be one derived from cytomegalovirus.

Regarding claim 44, a particular splice acceptor site is recited.

THE SPECIFICATION AND STATE OF THE ART REASONABLY CONVEY TO THE ARTISAN THAT THE INVENTORS WERE IN POSSESSION OF THE CLAIMED INVENTION

As held in In re Alton (76 F.3d 1168, 1172, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996), an adequate written description serves to ensure that the inventors had possession of the claimed subject matter. How the specification accomplishes that requirement is not material. Thus, ipsis verbis disclosure is not necessary, instead the disclosure need only reasonably convey to person skilled in the art that the inventor had possession of the subject matter in question.

At the outset, Appellants maintain that the Examiner has not established a prima facie case of unpatentability based on an insufficient written description for claims 1-4, 6-31, 35-37, 42 and 43.

There is no basis to conclude that an artisan on reading the instant specification teaching a splice acceptor site would not be reasonably convinced that the inventors were in possession of

a vector that contained a consensus splice acceptor site as claimed. The claimed invention clearly is within the scope of the disclosure.

The Examiner has not provided any substantiated argument or evidence to support the alleged unpatentability. The Examiner has not provided any evidence to support the conclusion that the instant description does not convey to one of ordinary skill in the art, who clearly was armed with the conventional knowledge of consensus splice sites at the time the application was filed, that the inventors were in possession of vectors containing a consensus splice acceptor site.

Hence, the Examiner has not discharged his duty of providing a reasoned statement of unpatentability. Accordingly, a prima face case of unpatentability has not been made.

On that basis alone, the rejection is legally insufficient, not proper and cannot stand. The rejection should be removed and the application passed to issuance.

But even if it were to be hypothesized that the Examiner had provided ample evidence to support a prima facie case of unpatentability based on written description, there is adequate evidence of record and reasoned argument of record to rebut any such hypothetical rejection.

As pointed out hereinabove with respect to the disputed claim element, the specification teaches that **a** splice acceptor site is included in a vector of interest. There is no limitation to what that splice acceptor site might be, whether it contains a consensus or not. Hence, contrary to the position of the Examiner, Appellants maintain that the use of the adjective, "consensus", is a more descriptive as compared to a broadening term.

As adequately documented in the evidence of record, it was well recognized before the application was filed that splice donor and splice acceptor sites can follow a pattern and yield a consensus sequence. As further testament that one of ordinary skill in the art would well recognize that a splice acceptor site could include a consensus sequence, attached hereto is a copy of pages from a reference that teaches that as of 1983, the art well recognized splice

acceptor consensus sequences. Hence, the notion of a consensus splice acceptor site was conventional in the art when the instant application was filed.

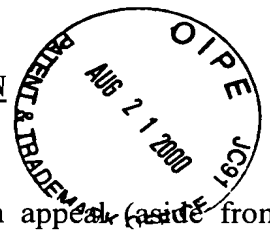
Armed with that information, it is clear an artisan would well recognize that the claimed invention, which relates to retrovirus vectors that contain a consensus splice acceptor site, is supported by a broad disclosure to splice acceptor sites in general.

Hence, even if it were to be hypothesized that a prima facie case of unpatentability had been made, Appellants have demonstrated with evidence and reasoned statements that one of ordinary skill in the art, armed with the conventional knowledge of splice consensus sequences, would be reasonably convinced that Appellants were in possession of the claimed invention when the application was filed. The claimed invention clearly is within the scope of the disclosure.

Accordingly, for that reason as well, the rejection cannot stand, must be removed and the application passed to issuance.

Regarding claim 44, as noted in the Office Action mailed 27 January 1999, page 3, line 1, and repeated in the Final Office Action mailed 19 July 1999, claims reciting MOV-9 are acceptable. Claim 44 does recite that specific splice acceptor site and thus incorrectly is included in the rejection.

Accordingly, claim 44 is allowable.



XI. CONCLUSION

It is clear the invention defined in the claims on appeal (aside from claim 44 that complies with the requirement of allowability as enunciated by the Examiner, are clearly described in the instant specification. The Examiner has not made out a prima facie case of unpatentability based on written description. Even if, arguendo, a prima facie case were made, there is ample evidence and reasoned argument to successfully rebut any such case. The instant specification reasonably convey to one of skill in the art that Appellants were in possession of the claim invention. Accordingly, the rejection must be removed and the application passed to allowance.

The instant Brief on Appeal is being filed in triplicate. Appellants hereby petition for any extension of time that may be required to maintain the pendency of the instant application, and any required fee for such extension is to be charged to Deposit Account No. 18-2220.

Respectfully submitted,

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APPENDIX

APPEALED CLAIMS

1. A recombinant retroviral vector useful to nonselectively transduce cells, comprising:

(a) a 5' LTR derived from a retrovirus of interest;

(b) a splice donor site located 3' to said 5' LTR;

(c) a Psi packaging site located 3' to said splice donor site;

(d) a consensus splice acceptor site located 3' to said Psi packaging site;

(e) an insertion site for a gene of interest located 3' to said consensus splice acceptor site;

(f) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site; and

wherein said vector does not contain a complete selectable marker gene used for the transduction of said cells, or a complete gag, env, or pol gene between said 5' and 3' LTR.

2. A recombinant retroviral vector according to Claim 1, said vector further comprising, a portion of a gag coding sequence adjacent to said Psi packaging site.

3. A recombinant retroviral vector according to Claim 2 wherein said gag coding sequence comprises, a splice donor site and a splice acceptor site, wherein said splice acceptor site is located upstream from a gene of interest inserted into said insertion site.

4. A recombinant retroviral vector according to Claim 3, said vector further comprising a transcriptional promoter functionally positioned such that a transcript of a nucleotide sequence inserted into said insertion site is produced, wherein said transcript comprises a gag 5' untranslated region.

6. A recombinant retroviral vector according to Claim 4, wherein said vector has all of the identifying characteristics of ATTCC 68,754.

7. A recombinant retroviral vector according to Claim 1, said vector further comprising a gene for expression inserted into said insertion site.

8. A recombinant retroviral vector according to Claim 7, wherein said gene for expression is selected from the group consisting of: a hormone, an enzyme, and a receptor.

9. A recombinant retroviral vector according to Claim 8, wherein said gene for expression encodes factor VIII or tPA.

10. A recombinant retroviral vector useful to nonselectively transduce cells, said vector comprising:

(a) a 5' LTR derived from a retrovirus of interest;

(b) a Psi packaging site located 3' to said 5' LTR;

(c) a consensus splice acceptor site located 3' to said Psi packaging site;

(d) an alpha globin transcriptional promoter located 3' to said Psi packaging site;

(e) an insertion site for gene of interest located 3' to said alpha globin transcriptional promoter;

(f) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site; and

wherein said vector does not contain a complete selectable marker gene used for transduction of said cells, or a complete gag, env, or pol gene between said 5' and 3' LTRs.

11. A recombinant retroviral vector according to Claim 10, said vector further comprising, a portion of the 5' untranslated region of the alpha-globin gene that is naturally joined to said alpha-globin transcriptional promoter.

12. A recombinant retroviral vector according to Claim 11, said vector further comprising, an enhancer sequence, wherein said enhancer is not in said 5' or 3' LTR.

13. A recombinant retroviral vector according to Claim 12, wherein an enhancer sequence is located upstream from said transcriptional promoter.

14. A recombinant retroviral vector according to Claim 13, wherein said enhancer sequence is a cytomegalovirus enhancer sequence.

15. A recombinant retroviral vector according to claim 14, wherein said vector has all of the identifying characteristics of ATCC No. 68755.

16. A recombinant retroviral vector according to Claim 10, wherein said 3' LTR does not contain a functional enhancer sequence.

17. A recombinant retroviral vector according to Claim 10, said vector further comprising, a gene for expression inserted into said insertion site.

18. A recombinant retroviral vector according to Claim 10, wherein said gene for expression is selected from the group consisting of a hormone, an enzyme, and a receptor.

19. A recombinant retroviral vector according to Claim 18, wherein said gene for expression encodes factor VIII or tPA.

20. A recombinant retroviral cell line wherein said cell line has been transfected with the coding sequence of a retroviral vector of one of Claims 1 to 19.

21. A recombinant retroviral vector useful to nonselectively transduce cells, comprising, a 5' LTR derived from a murine leukemia virus, a consensus splice acceptor site and an insertion site for a gene of interest located between said 5' and 3' LTRs, wherein said vector does not contain a complete selectable marker gene used for the transduction of said cells, or a complete gag, env, or pol gene.

22. The recombinant retroviral vector of Claim 21, further comprising an exogenous enhancer.

23. The recombinant retroviral of Claim 22, wherein the exogenous enhancer is derived from a myeloproliferative sarcoma virus.

24. The recombinant retroviral vector of Claim 22, wherein the exogenous enhancer is derived from Moloney Friend Virus.

25. The recombinant retroviral vector of Claim 21, 22, 23, or 24, further comprising a B2 mutation..

26. The recombinant retroviral vector of Claim 21, 22, 23 or 24, wherein the 3' LTR is replaced with a 3' LTR derived from a myeloproliferative sarcoma virus.

27. The recombinant retroviral vector of Claim 26, further comprising a B2 mutation.

28. The recombinant retroviral vector of Claim 21, 22, 23 or 24, whrein the 5' LTR is replaced with a 5' LTR derived from a myeloproliferative sarcoma virus.

29. The recombinant retroviral vector of Claim 28, further comprising a B2 mutation.

30. The recombinant retroviral vector of Claim 21, 22, 23, or 24, whrein both the 5' LTR and a 3' LTR are respectively replaced with a 5' LTR and a 3' LTR derived from a myeloproliferative sarcoma virus.

31. The recombinant retroviral vector of Claim 30, further comprising a B2 mutation.

35. A recombinant retroviral particle produced by a producer cell comprising the recombinant retroviral vector of claim 1 said particle having the property of being capable of transducing mammalian cells.

36. A particle according to claim 35, 42 or 43 wherein said transducing occurs in vitro.

37. A particle according to claim 35, 42 or 43 wherein said transducing occurs in vivo.

42. A recombinant retroviral particle produced by a producer cell comprising the recombinant retroviral vector of claim 10, said particle having the property of being capable of transducing mammalian cells.

43. A recombinant retroviral particle produced by a producer cell comprising the recombinant retroviral vector of claim 21, said particle having the property of being capable of tranducing mammalian cells.

44. A recombinant retroviral vector useful to nonselectively transfect cells, comprising:

(g) a 5' LTR derived from retrovirus of interest;

(h) a splice donor site located 3' to said 5' LTR;

(i) a Psi packaging site located 3' to said splice donor site;

(j) a consensus splice acceptor site, derived from MOV-9, located 3' to said Psi packaging site;

(k) an insertion site for a gene of interest located 3' to said consensus splice acceptor site;

(l) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site; and wherein said vector does not contain a complete selectable marker gene used for the tranfection of said cells, or a complete gag, env, or pol gene between said 5' and 3' LTR.